IMPORTANT IMMUNOLOGIC CHECKPOINTS IN BREAST CANCER IN FEMALE DOGS

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INTRODUCTION

Breast cancer is the most frequent tumor in the clinical of dogs. The immunologic system play an important role in the progression of the tumor and survival of patients, but the tumor immunoedition allows the tumor to scape it, which promote the exhausted of the T lymphocytes. Immunotherapy against some immunologic checkpoints, such as PD-1/PD-L1 pathway, may reverse de T cell dysfunction.

AIMS

The aim of the study is to deepen in the action of antitumor immune system in the breast canine cancer, know the importance in the diagnosis, prognosis and survival patients and understand the role of the PD-1/PD-L1 pathway.

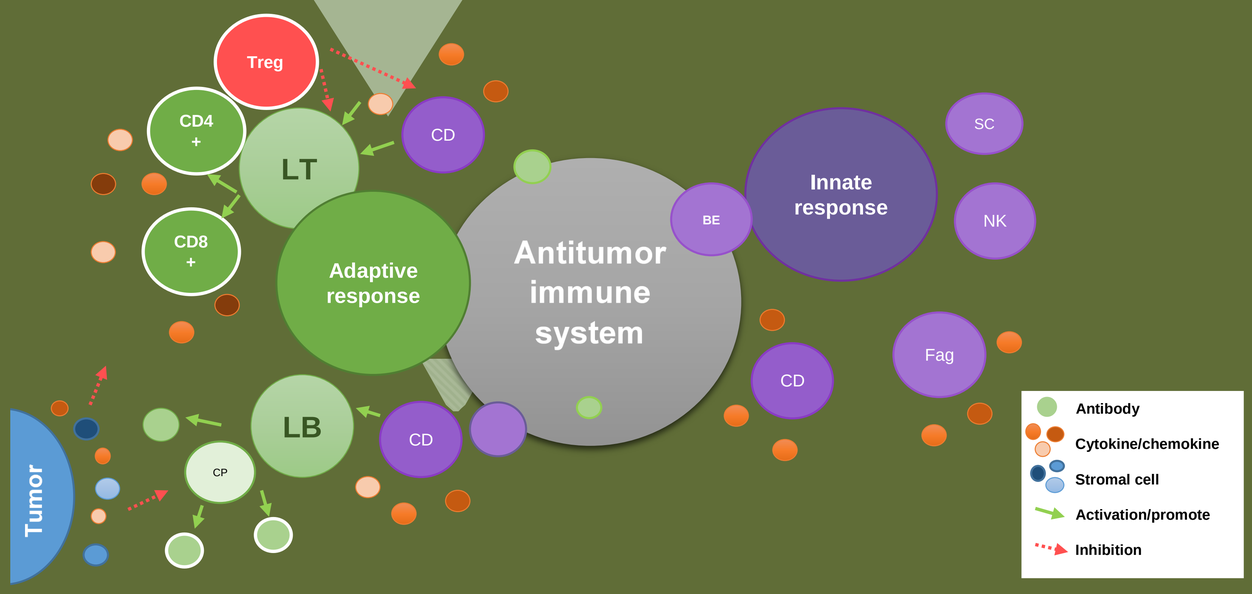

Figure 1. T cells with dendritic cells and cytokines play an important role in the antitumor response, but cytokine can also inactivate acquired response, as well as regulatory T cells and stromal cells of the tumor (*LT, T lymphocyte; LB, B cell; CP, plasma cell; CD, dendritic cell; Fag, phagocyte (neutrophils and macrophages); NK, natural killer; BE, epithelial barrier).*

T cells infiltrate in Canine mammary tumors

Table 1. Studies of T-lymphocyte infiltrate in Canine mammary tumors (Carvalho *et al.*, 2014).

Author	Year	Patients (n)	Type	Comments
Estela-Lima et al.	2010	51	T-lymphocyte infiltration	Animals with high proportions of CD4+ and low CD8+ T-cells had lower survival rates
Kim et al.	2010	58	T-lymphocyte infiltration	Association between the expression of TILs, cytokines, and mutation of BRCA1 suggests that all of these factors may play a role in tumor progression
Carvalho et al.	2011	57	T-lymphocyte infiltration	Tendency for an association of a higher number of CD3+ TILs and a shorter overall survival. CD3+ T-lymphocytes in the adnexal nontumoral mammary gland revealed a statistically significant relationship with overall survival.
Saeki et al.	2012	140	Lymphocyte infiltration	Relationship of TILs and canine mammary tumors malignancy.
Kim et al.	2012	37	Regulatory T-cells (Treg)	The number of Treg cells is increased in tumors with poor prognostic factors, such as high histological grade, lymphatic invasion, and necrosis.
Kim et al.	2013	47	Lymphocyte infiltration	Intense lymphocyte infiltration was associated with aggressive histologic features (higher histologic grade; lymphatic invasion).

Expression of PD-1/PD-L1 pathway

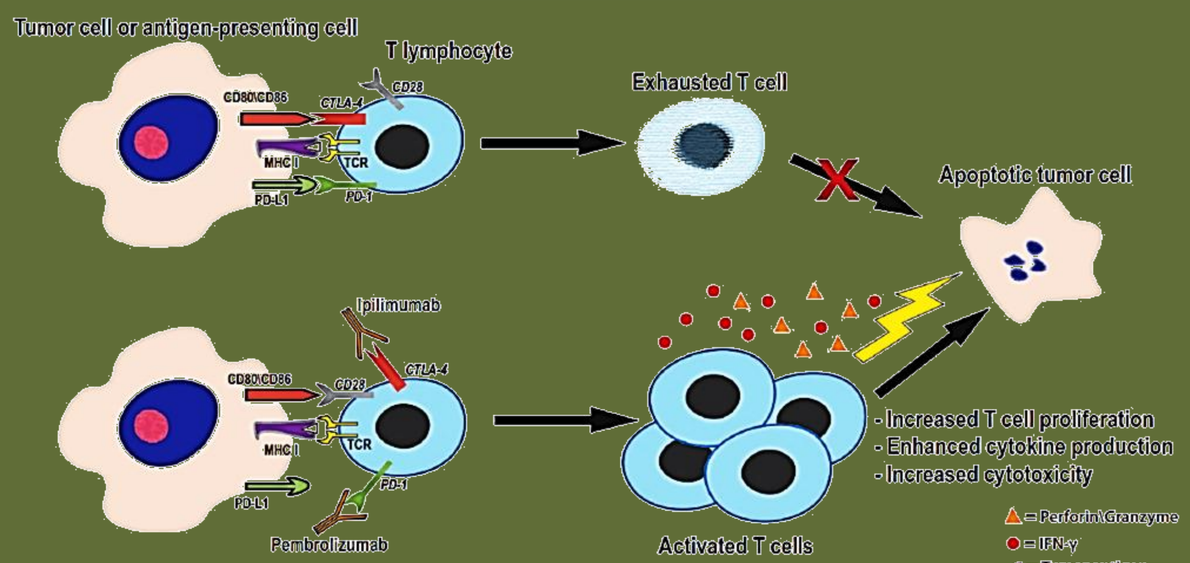

Figure 2. T cells can be exhausted for PD-1/PD-L1 pathway but it can be reverse with a blockade of this pathway by checkpoints inhibitors, allowing T cell activation and promoting apoptosis of tumor cell (Regan *et al.*, 2016).

Similarities between human and canine mammary tumors

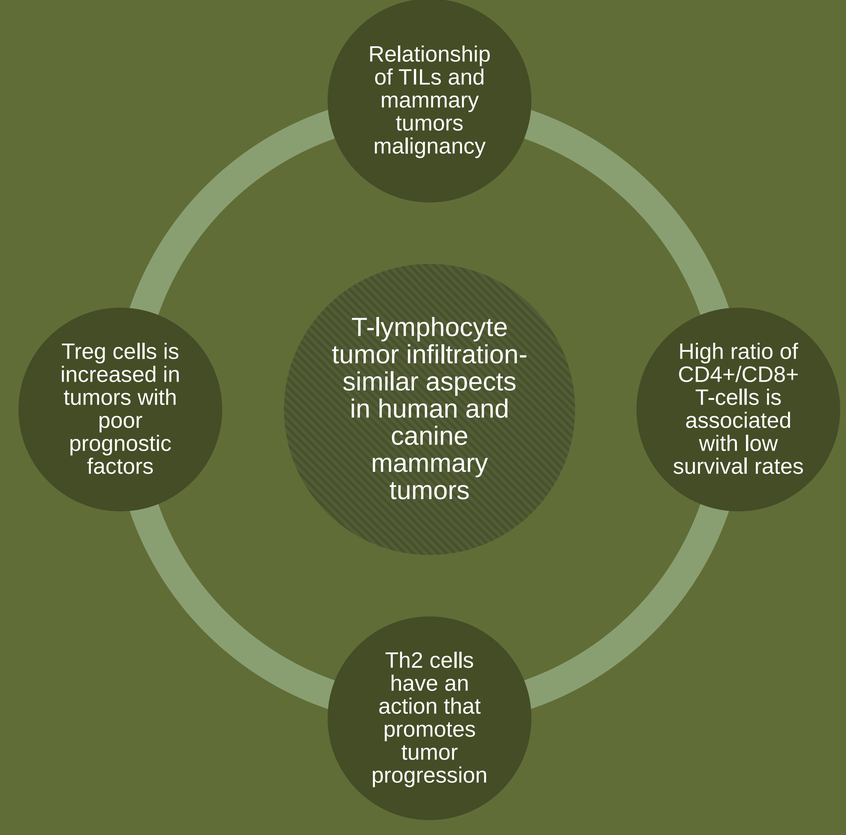

Figure 3. Similarities of T-lymphocyte tumor infiltration in human and canine mammary tumors (Carvalho *et al.*, 2014).

T cells exhausted revives with the PD-1/PD-L1 pathway blockade

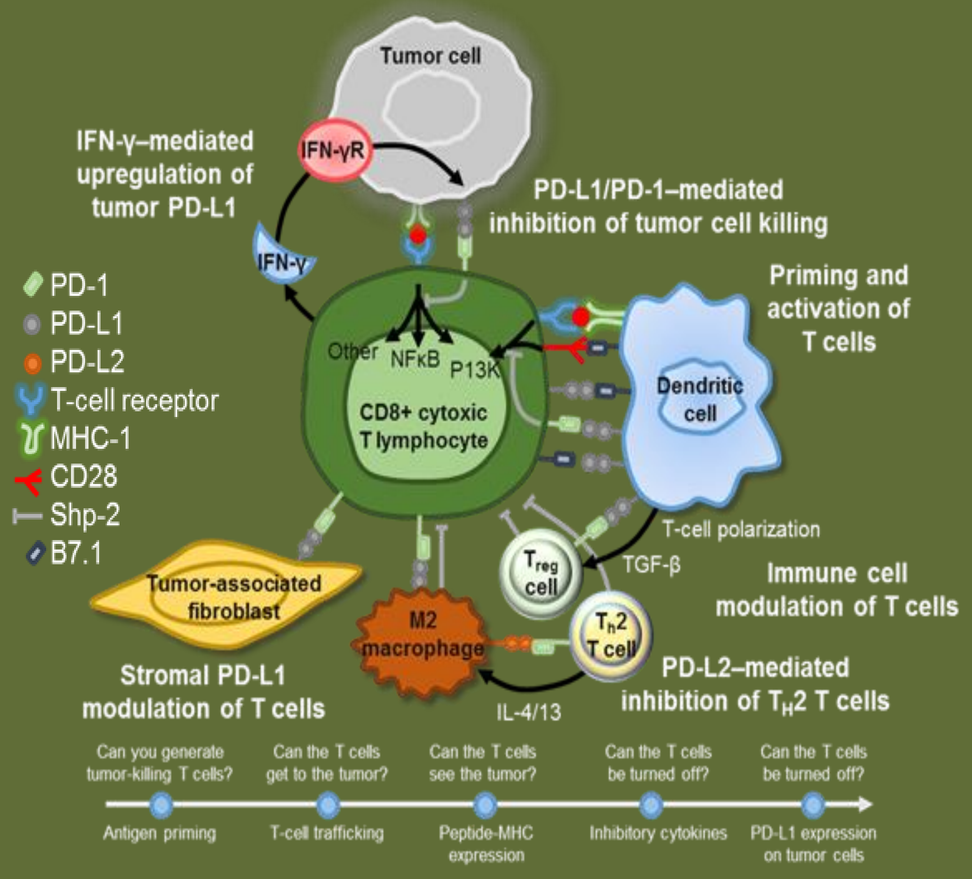

Figure 4. The scheme shows the molecules involved in the activation and modulation of T cells, as well as the involvement of PD-1/DP-L1 pathway in all processes (Sznol Mand L Chen, 2013).

CONCLUSIONS

- Need to clarify the role of the inflammatory infiltrate and participation of the different subtypes of T cells in tumor progression, prognosis and survival of patients.
- Many similarities in canine and human breast cancer makes a dog a model in human oncology.
- Tumoral resistance is possible with overexpression of PD-L1 by cytokines such as IFN-γ, being PD-L1 a biomarker of poor prognosis, but is not considered an absolute one.
- Immunotherapy is opening the way to a new therapeutic strategy, finding satisfactory results in human oncology, but more studies in mammary canine cancer are required to finding an effective treatment.

REFERENCES

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